Respiratory Medicine (2000) **94,** 1029–1037
doi:10.1053/rmed.2000.0927, available online at http://www.idealibrary.com on IDEAL®

Original Articles

The safety and efficacy of short course (5-day) moxifloxacin *vs*. azithromycin in the treatment of patients with acute exacerbation of chronic bronchitis

C. A. DeAbate*, C. P. Mathew†, J. H. Warner‡ A. Heyd‡ and D. Church‡

**Medical Research Centers, New Orleans, Louisiana, †Westbank Research Centers, Gretna, Louisiana and ‡Bayer Corporation, West Haven, Connecticut, U.S.A.*

Chronic bronchitis is common among adults and infectious exacerbations contribute considerably to morbidity and mortality. We aimed to compare the safety and efficacy of moxifloxacin to azithromycin for the treatment of patients with acute exacerbations of chronic bronchitis (AECB) of suspected bacterial origin.

Between October 1998 and April 1999, 567 patients with AECB were enrolled at 37 centers across the United States and Canada of which 280 (49%) had acute bacterial exacerbation of chronic bronchitis (i.e. pretherapy pathogen).

Patients were randomized to either oral moxifloxacin 400 mg administered once daily for 5 days or azithromycin for 5 days (500 mg qd × 1, then 250 mg qd × 4). For the purpose of study blinding, all patients received encapsulated tablets.

The main outcome measure was clinical response at the test-of-cure visit (14–21 days post-therapy). Secondary measures included bacteriologic response and a time-course of bacteriological eradication (one center only). Three patient populations were analysed for efficacy: clinically-valid, microbiologically-valid (i.e. those with a pretherapy pathogen), and intent-to-treat (i.e. received at least one dose of study drug).

For the efficacy-valid group, clinical response at the test-of-cure visit was 88% for patients in each treatment group. In 237 microbiologically-valid patients, corresponding clinical resolution rates were 88% for 5-day moxifloxacin *vs*. 86% for 5-day azithromycin. Bacteriological eradication rates at the end of therapy were 95% for 5-day moxifloxacin and 94% for the azithromycin group. Corresponding eradication rates at the test-of-cure visit were 89% and 86%, respectively. Of note, eradication rates at test-of-cure for *Haem. philos influenzae* and *H. parainfluenzae* for moxifloxacin were 97% and 88% compared to 83% and 62% respectively for azithromycin. Among 567 intent-to-treat patients (283 moxifloxacin and 284 azithromycin), drug-related events were reported for 22% and 17%, respectively. Diarrhea and nausea were the most common drug-related events reported in each treatment group.

Moxifloxacin 400 mg once daily for 5 days was found to be clinically and bacteriologically equivalent to 5-day azithromycin for the treatment of AECB of proven bacterial etiology. Given its excellent *in-vitro* activity, especially against antibiotic-resistant respiratory pathogens, and its acceptable safety profile, moxifloxacin should be considered an effective alternative therapy for patients with AECB of suspected bacterial origin.

Key words: moxifloxacin; ABECB; short-course therapy.

Respir. Med. (2000) **94,** 1029–1037

Introduction

Acute exacerbation of chronic bronchitis (AECB) is responsible for a significant amount of patient morbidity. Approximately 50% of patients who experience acute exacerbations will have at least two episodes per year (1,2). Furthermore, approximately one in five patients with AECB will require hospitalization for any given episode (3).

Received 13 March 2000 and accepted 19 May 2000. Published online 8 September 2000.

Correspondence should be addressed: C.A. DeAbate MD, Medical Research Centers, 1020 Gravier Street, Suite 100, New Orleans, Louisiana 70112, U.S.A.

Although the precipitating event leading to AECB is often unknown, viral or bacterial infection is a common cause (4). *Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pneumoniae* are responsible for the majority of bacterial episodes (4,5). Although these pathogens may be isolated during periods of quiescence, quantitative cultures have demonstrated an increase in these pathogens during an acute exacerbation (6,7). In patients experiencing multiple exacerbations per year, not only are these three core organisms likely to be causing infection, but Gram-negative bacilli (e.g. *Klebsiella pneumoniae, Pseudomonas aeruginosa*) become more probable. In any event, the presence of pathogenic bacteria in the bronchial airways can precipitate progressive airway deterioration and

0954-6111/00/111029+09 $35·00/0

ultimately lead to deterioration in lung function. As such, the major goals of therapy are to provide rapid clinical resolution, eradicate the causative pathogens, and to promptly return the patient's respiratory function to their pre-exacerbation baseline.

Over a decade ago, Anthonisen *et al.* reported that antimicrobials appeared to be beneficial in patients with AECB compared to those given placebo (8). His study also showed that antimicrobials were most effective for patients categorized as having type I symptoms (i.e. presence of dyspnea, increased sputum volume, sputum purulence). A meta-analysis of published randomized antimicrobial trials given for AECB (1955–1994) has recently confirmed Anthonisen's original findings (9). During the last two decades, doxycycline, TMP/SMX, and beta-lactams have been commonly prescribed for patients experiencing an acute exacerbation (4).

In the outpatient setting, current managed care practices have limited the physician's ability to determine whether an AECB is secondary to a bacterial etiology (i.e. sputum cultures are infrequently obtained). Accordingly, empiric antimicrobial therapy is often prescribed for suspected acute bacterial exacerbations of chronic bronchitis (ABECB). The selection of empirical antimicrobial treatment must consider a number of factors including the potential bacterial etiologies, the likelihood of drug-resistant organisms, the severity of the infection, underlying co-morbidities, and the need for hospitalization.

A recent challenge in the treatment of ABECB is the emergence of resistance to traditional antibiotics amongst the commonly isolated respiratory pathogens. The overall prevalence of beta-lactamase production has been reported for approximately 35% of *H. influenzae* isolates and $>90\%$ of *M. catarrhalis* isolates (10,11). Other recent surveillance studies have reported that approximately 25–45% of *S. pneumoniae* isolates are penicillin-resistant, of which high level resistance accounts for almost one-third of all isolates (10,12–14). Although penicillin resistance is of interest, it is more significantly a marker for beta-lactam and macrolide resistance; however, little cross-resistance has been noted among the fluoroquinolones (15). Based on these findings, new alternative therapies that are highly effective against the key respiratory pathogens are needed to combat the rising level of antimicrobial resistance, especially multiple antibiotic-resistant *S. pneumoniae*.

The main purpose of the current trial was to compare the efficacy and safety of a 5-day moxifloxacin *vs.* 5-day azithromycin regimen in the treatment of outpatients with AECB of suspected bacterial origin. A secondary objective of the study was to compare the rate of bacteriologic eradication between moxifloxacin and azithromycin.

Methods

STUDY DESIGN AND ANTIMICROBIAL THERAPY

This was a prospective, double-blind, randomized, multicenter trial designed to compare moxifloxacin to azithromycin in the treatment of patients with AECB. Patients were randomized in blinded fashion at the first visit in a 1:1 ratio to moxifloxacin 400 mg once daily for 5 days (Bayer Pharmaceutical, West Haven, CT, U.S.A.) or azithromycin 500 mg once daily for the first day (loading dose), followed by 250 mg once daily for a total of 4 days (Pfizer Inc, New York, NY, U.S.A.) based on a randomization code that was computer-generated by Bayer Corporation. Following random assignment to treatment, all patients took two encapsulated tablets once daily on day 1 (patients randomized to moxifloxacin received one active and one placebo tablet), followed by one encapsulated tablet on days 2–5. Study drug was taken at approximately the same time of day with 120 ml of water, with or without food. At the end of therapy, each patient was questioned regarding the number of capsules taken during the treatment period and a pill count performed in order to document patient compliance.

STUDY POPULATION

Patients eligible for inclusion in the study were outpatients at least 18 years old with a suspected ABECB. Underlying chronic bronchitis was defined as the daily production of sputum on most days for at least 3 consecutive months and for more than 2 consecutive years. Patients with a diagnosis of chronic obstructive pulmonary disease (COPD) were also eligible for enrollment. Patients with mild to moderate respiratory exacerbations were entered into the study and categorized as types I, II or III [as defined by Anthonisen *et al.* (8) and the American Thoracic Society (16)]. The acute nature of the infection was documented by recent increases of bronchopulmonary symptoms and laboratory evidence of an acute lower respiratory tract bacterial infection. All study participants were required to have had increased purulent/mucopurulent sputum and at least one of the following: increased cough, increased dyspnea, increase of sputum volume, or presence of fever (oral temperature $>38^{\circ}$C).

Patients were excluded for the following reasons: allergy or severe adverse reactions to carboxyquinolone derivatives or azalide/macrolide derivatives; previous history of fluoroquinolone-related tendinopathy; unable to take oral medication; pregnancy or lactating; chest X-ray suggestive of a new pneumonia; recent diagnosis or unresolved lung or chest cavity malignancy; neutrophil count $>1000\,\mathrm{mm}^{-3}$, CD4 count $>200\,\mathrm{mm}^{-3}$ or other evidence of significant immunosuppression; evidence of significant liver impairment (AST, ALT or total bilirubin more than three times upper limit of normal); renal insufficiency requiring dialysis; history of QT_c prolongation; or a need for a concomitant antibacterial agent with a spectrum of activity similar to the study drugs. Prospective patients were also excluded if they received drugs known to affect QT interval (e.g. amiodarone, sotalol, terfenadine); or received previous therapy with a systemic antibiotic for more than 24 h prior to enrollment. Adjunctive medications including bronchodilators, mucolytics, or expectorants were permitted according to usual physician practice in each treatment group. The study was

approved by each investigator's institutional review board and all patients provided written informed consent prior to enrollment.

CLINICAL BACTERIOLOGIC AND SAFETY ASSESSMENTS AND DEFINITIONS

Clinical response

A clinical response was determined at both the end of therapy (0–6 days post-therapy) and at the test-of-cure (14–21 days post-therapy) evaluations. Clinical response was based on serial examinations of the patient using the following parameters: objective signs of auscultatory findings (rales, rhonchi, wheezing, breath sounds); prolongation of expiratory phase; presence of fever $>38^{\circ}C$; presence of WBC $>12\,000$ cells mm^{-3}; subjective symptoms of chest pain or discomfort; change in cough frequency and severity; sputum characteristics (thickness and volume); dyspnea. At the end of therapy, clinical response was graded as *clinical cure* [disappearance of acute signs and symptoms related to the infection (complete return to a stable pre-exacerbation condition) or sufficient improvement such that additional or alternative antimicrobial therapy was not required], *clinical failure* (insufficient lessening of the signs and symptoms of infection such that additional or alternative antimicrobial therapy was required), or *indeterminate* (clinical assessment was not possible to determine for any reason). The clinical response at the test-of-cure visit was reported as: *continued clinical cure* (disappearance of acute signs and symptoms of infection or continued improvement where additional or alternative antimicrobial therapy was not required), *clinical recurrence* (reappearance of signs and symptoms of AECB considered related to a bacterial process such that reinstitution of antimicrobial therapy was required), or *indeterminate* (patients in whom a clinical assessment was not possible to determine). In addition, *clinical failure* at the test-of cure visit was considered in patients with either an end of therapy evaluation of failure or a follow-up evaluation of recurrence.

Bacteriologic Response

Bacteriologic evaluation (Gram stain and sputum culture) was performed pretherapy, during therapy (days 1–5), at the end of therapy visit (post-therapy days 0–6) and at the test-of-cure visit (post-therapy days 14–21). For all isolated organisms, E-test susceptibility testing were performed for azithromycin according to NCCLS guidelines; an MIC >2 mcg ml^{-1} was considered a borderline result for moxifloxacin (17,18). *Haemophilus* spp. and *M. catarrhalis* also were tested for beta-lactamase production. *S. pneumoniae* was tested for penicillin susceptibility, either by oxacillin disk or by penicillin E-test strip.

During therapy (treatment days 1–5), patients at one center were asked to return to the investigator's clinic on a daily basis in order to provide a sputum specimen for culture. For patients unable to return on a daily basis, instructions were provided on the proper production and storage of sputum specimens. Sputum specimens collected on this basis were stored under conditions of refrigeration for not longer than 24 h prior to culture and Gram stain. Culture and Gram-stain results were recorded on a daily basis for each specimen along with the date of eradication of the causative organism(s). The date of eradication was defined as the earliest date on which there were two successive negative cultures.

At the end of therapy the bacteriological responses were graded as eradication, presumed eradication (if no material was available due to a clinical success), persistence, presumed persistence (no material was available in a patient considered a clinical failure) or indeterminate (if bacteriological response to the study drug was not evaluable for any reason). In addition, a superinfection was defined as the appearance of a new organism in a patient who was symptomatic. For patients with an end of therapy response of eradication or presumed eradication, test-of-cure bacteriologic eradication was defined as: continued eradication, presumed continued eradication, eradication with relapse (original causative organism absent at end of therapy, but reisolated at test-of-cure), eradication with reinfection (original organism eradicated, but new causative organism identified) and indeterminate (not evaluable for any reason).

Safety

All patients receiving at least one dose of study drug were evaluable for safety (intent-to-treat population). Safety was evaluated on the basis of physical examination findings, ECGs, adverse events, intercurrent illness and laboratory tests, including routine hematology, blood chemistry and urinalysis tests. Investigators rated each adverse event subjectively according to relationship to study drug (probable, possible, remote, or none) and severity (mild, moderate, severe, or serious or life-threatening).

EFFICACY ANALYSES

Three populations of patients were analysed for efficacy in this study: patients considered valid for clinical efficacy (defined below), those considered microbiologically valid (i.e. patient valid for clinical efficacy with a causative bacteria isolated and identified within 48 h before onset of therapy), and patients valid for safety (i.e. any patient who has received at least one dose of study drug).

For a course of therapy to be judged valid for clinical efficacy, the following criteria were mandated: AECB confirmed both by appropriate history of underlying disease and presentation with symptoms of acute infection; all inclusion/exclusion criteria met; study drug given for at least 48 h if a clinical failure, or for at least 4 days if a clinical success; no concurrent administration of non-study antimicrobial agents, unless the patient was a treatment failure or had recurring infection; and at least 80% compliance with study drug regimen.

STATISTICAL ANALYSES

The primary objective of the study was to determine if 5-day moxifloxacin was equivalent to 5-day azithromycin therapy, in terms of the rate of clinical resolution at the test-of-cure visit. Bacteriologic response was a secondary objective. Using the normal approximation to the binomial distribution, true clinical failure rates of 10% in both treatment groups, a lower limit of equivalence of 10% for the difference between treatments, and a one-sided alpha of 0·025, the 221 valid patients in the moxifloxacin group and the 243 valid patients in the azithromycin group provided 95% power to reject the null hypothesis of inequivalence. Power would be higher for the analysis using Mantel–Haenszel weights.

For categorical demographic and baseline medical characteristics, a chi-squared test was used to test for the differences between the two treatment groups. For continuous variables, a one-way analysis of variance was used, with a term included for treatment.

For each evaluation of clinical and bacteriologic response, a two-sided 95% confidence interval (CI) for the weighted difference between treatment groups was constructed using Mantel–Haenszel weights (weighting by center). Equivalence was defined as the lower limit of the two-sided 95% CI for the difference between groups being greater than -10%.

A comparison of the timecourse of bacteriologic eradication between treatment groups was also evaluated at one site. The presence of causative bacteria was assessed once per day during therapy in each patient and the data analysed using exact contingency table methods.

Comparisons of the incidence rates of adverse events between the two study drug groups were done descriptively. Events were tabulated by type (according to the COSTART glossary) and frequency for all adverse events and for those events considered to be related to drug treatment.

Results

STUDY POPULATION

Five hundred and sixty-seven adults with AECB were enrolled at 37 clinical sites and comprised the safety (intent-to-treat) population (283 moxifloxacin, 284 azithromycin). The clinically-valid population included 464 patients (221 moxifloxacin, 243 azithromycin), of which 237 (119 moxifloxacin, 118 azithromycin) patients made up the microbiologically-valid group. One hundred and three patients were excluded from the clinical efficacy-valid analysis (62 moxifloxacin, 41 azithromycin). Reasons for exclusion included: essential data missing or invalid ($n=69$), entry criteria violations ($n=13$), inadequate duration of treatment ($n=11$), use of prohibited pre- or post-therapy medications ($n=7$) and lost-to-follow-up ($n=3$). The primary reasons for disqualification were similar between the two study drug groups.

The baseline demographics and medical characteristics of the clinically-valid efficacy patient population were similar between the two treatment groups (Table 1). There were no statistically significant differences between treatment groups with respect to age, sex, or race. Over 75% of patients in both treatment groups were active cigarette smokers. The majority of patients in each treatment group had type 1 severity of infection ($>70\%$) (Table 1). A mean of 2·2 AECB episodes were reported during the past 12 months for both study drug groups combined. Baseline demographic and medical characteristics in the safety and microbiologically-valid groups were similar to those in the clinically-valid population.

Clinical signs and symptoms present at study entry for the clinically efficacy-valid patients revealed that greater than half of moxifloxacin- and azithromycin-treated patients had greatly increased cough frequency, sputum production and sputum thickness, as well as evidence of

Table 1. Demographics and baseline medical characteristics: clinically-valid population

Variable	Moxifloxacin ($N=221$)	Azithromycin ($N=243$)
Age, years		
Mean ± SD	53·9 ± 14·5	54·5 ± 15·7
Range	19–88	20–86
Sex, *n* (%) male	120 (54)	135 (56)
Race, *n* (%) Caucasian	142 (64)	163 (67)
Type of AECB infection as per Anthonisen (8), *n* (%)		
I	171 (77)	178 (73)
II	47 (21)	63 (26)
III	3 (1)	2 (<1)
Mean number of exacerbations in past 12 months	2·3	2·2
History of cigarette smoking, past or present, *n* (%)	188 (85)	190 (78)
Current cigarette smoker, *n* (%)	117 (53)	119 (49)
Mean length of history (years)	30·1	31·6
Mean number cigarettes smoked per day	25·9	26·1

*Includes patients who had pretherapy pathogen.

rhonchi and wheezing on chest examination. In addition, approximately one-third of moxifloxacin- and azithromycin-treated patients had greatly increased dyspnea, decreased breath sounds, and prolongation of their expiratory phase compared to their pre-exacerbation baseline condition.

TREATMENT EFFICACY

Clinical response

For the clinically efficacy-valid population, clinical cure at the end of therapy (0–6 days post-therapy) was reported in 90% of moxifloxacin- and 92% of azithromycin-treated patients (Table 2). At the test-of-cure evaluation, 88% of patients in each group were clinically cured (Table 2). Recurrence was reported for seven moxifloxacin- and 10 azithromycin-treated patients. Altogether, 27 moxifloxacin- and 29 azithromycin-treated patients were categorized as clinical failures at test-of-cure. Among the 27 moxifloxacin treatment failures, four patients achieved bacteriologic eradication and 10 had presumed or documented persistence. For the 29 azithromycin failures, three had eradication, two had eradication with recurrence and 11 were presumed or known persisters. The remainder of clinical failures in both treatment groups did not have valid bacteriological responses due to the absence of an identifiable pathogen pretherapy. Exploratory analyses failed to reveal any clinically significant differences in response rates based on demographic or baseline medical characteristics (data not shown).

Statistical equivalence between the moxifloxacin and azithromycin 5-day treatment regimens was also established for clinical efficacy in the intent-to-treat population (Table 2).

Bacteriologic Response

Among 567 patients enrolled, 280 (49%) patients had at least one pretherapy organism isolated and identified prior to initiation of study drug therapy. Of these 280 patients, 237 patients were also valid for efficacy and were said to be microbiologically-valid, from which a total of 259 causative bacteria (133 moxifloxacin, 126 azithromycin) were isolated and identified. Fifteen patients in the moxifloxacin group and six patients in the azithromycn group each had two causative organisms isolated and identified; one additional azithromycin patient had three organisms identified at enrollment. The most commonly isolated organisms in the microbiologically-valid group were *H. influenzae* [71 (27%)], *M. catarrhalis* [49 (19%)], *S. pneumoniae* [39 (15%)], and *H. parainfluenzae* [29 (11%)]. While none of the pretherapy isolates were resistant to moxifloxacin, 36 isolates were resistant to azithromycin. Of the common respiratory pathogens, 13 *H. influenzae* isolates were azithromycin-resistant, six isolates of *S. pneumoniae* were azithromycin-resistant, and nine *H. parainfluenzae* isolates were azithromycin-resistant.

Analyses for bacteriologic response at the end of therapy, including presumed eradication, also revealed similar response rates between the study drug regimens (96% moxifloxacin and 94% azithromycin; Fig. 1). At the end of therapy, five bacteria in the moxifloxacin group were found to be persistent or presumed persistent, including two *Pseudomonas* spp., two *Stenotrophomonas maltophilia*, and one *Alcaligenes* sp. Azithromycin, on the other hand, failed to eradicate seven of the more common respiratory

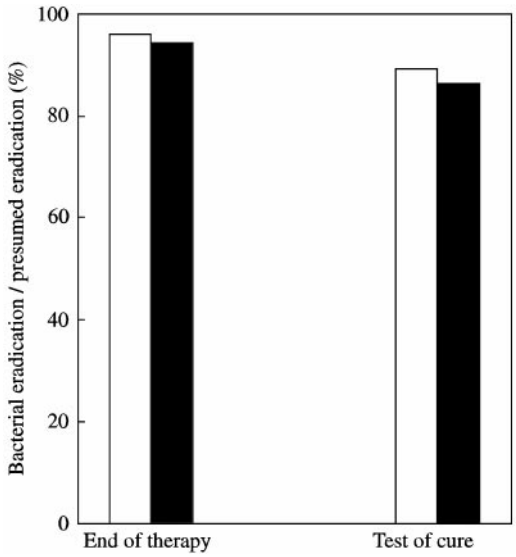

FIG. 1. Eradication/presumed eradication rates for microbiologically-valid population. □ moxifloxaxin; ■ zithromycin.

TABLE 2. Clinical cure rates

	Clinically-valid		Microbiologically-valid		Safety	
	Moxifloxacin *n/N* (%)	Azithromycin *n/N* (%)	Moxifloxacin *n/N* (%)	Azithromycin *n/N* (%)	Moxifloxacin *n/N* (%)	Azithromycin *n/N* (%)
End of therapy (0–6 days post-therapy)	192/212 (91)	208/227 (92)	106/116 (91)	104/115 (90)	228/252 (90)	239/261(92)
Test-of-cure (14–21 days post-therapy)	194/221 (88)	214/243 (88)	105/119 (88)	102/118 (86)	203/237 (86)	218/250 (87)

Table 3. Eradication rates for the most commonly isolated pretreatment organisms

	End of therapy		Test-of-cure	
	Moxifloxacin *n/N* (%)	Azithromycin *n/N* (%)	Moxifloxacin *n/N* (%)	Azithromycin *n/N* (%)
Haemophilus influenzae	34/34 (100)	33/36 (92)	34/35 (97)	30/36 (83)
Moraxella catarrhalis	29/29 (100)	20/20 (100)	29/29 (100)	20/20 (100)
Haemophilus parainfluenzae	16/16 (100)	10/13 (77)	14/16 (88)	8/13 (62)
Streptococcus pneumoniae	17/17 (100)	19/19 (100)	16/18 (89)	18/21 (86)
Staphylococcus aureus	8/8 (100)	7/7 (100)	8/8 (100)	7/7 (100)

Table 4. Drug-related adverse events occurring in at least 2% of patients

Adverse event	Moxifloxacin *n* (%) $N = 283$	Azithromycin *n* (%) $N = 284$
Abdominal pain	5 (2)	7 (2)
Headache	6 (2)	5 (2)
Asthenia	5 (2)	1 (<1%)
Nausea	15 (5)	9 (3)
Diarrhea	13 (5)	19 (7)
Dry mouth	5 (2)	4 (1)
Dizziness	9 (3)	3 (1)

organisms including three *H. influenzae*, three *H. parainfluenzae* and one *P. aeruginosa*. The eradication rates at the end of therapy for the most commonly isolated pretherapy bacteria may be found in Table 3. For these key respiratory pathogens moxifloxacin eradicated 100% of organisms compared to 77–100% eradication following azithromycin therapy. Superinfections were reported for three moxifloxacin-treated patients and were due to one each of *Serratia marcescens, Alcaligenes* sp. and *H. influenzae*, whereas twice as many azithromycin-treated patients experienced a superinfection (*Staphylococcus aureus* × 2, *S. pneumoniae* × 2 and one each of *Pseudomonas* sp., *H. influenzae* and *H. parainfluenzae*).

At the test-of-cure evaluation, continued and/or presumed eradication was reported in 89% of moxifloxacin- and 86% of azithromycin-treated patients (95% CI = −6·14, 11·24). A recurring infection was experienced by one moxifloxacin (*Klebsiella pneumoniae*) and two azithromycin patients (*H. influenzae, H. parainfluenzae*). A reinfection was reported for one moxifloxacin patient (*Cedecea apagei*) and five azithromycin patients (two *H. influenzae* and one each of *K. pneumoniae, P. aeruginosa* and *H. parahemolyticus*). The eradication rates at the test-of-cure visit for the most commonly isolated pretherapy bacteria are outlined in Table 3. Eradication rates were similar except for *Haemophilus* spp., wherein moxifloxacin eradicated 94% of all organisms compared to 78% in azithromycin-treated patients.

Time-course to bacteriological eradication

Data were collected only for microbiologically-valid patients from a single center. Eradication of the original causative organism was achieved by day 3 in 17 of 27 (63%) moxifloxacin- and 13 of 27 (48%) azithromycin-treated patients ($P = 0{\cdot}11$). One additional patient in each treatment group achieved bacteriologic eradication by day 4. Two additional patients given azithromycin had their pretherapy pathogen eradicated by day 5. In addition, nine patients from the moxifloxacin group and seven patients in the azithromycin group achieved eradication for the first time at end of therapy. None of the moxifloxacin-treated patients but four patients in the azithromycin group had persistent infections at end of therapy.

SAFETY AND ADVERSE EVENTS

One hundred and sixteen (41%) moxifloxacin- and 108 (38%) azithromycin-treated patients reported at least one treatment-emergent adverse event. Of these, drug-related adverse events, as assessed by the investigator, were reported in 61 (22%) moxifloxacin and 49 (17%) azithromycin patients. The rates of specific drug-related events were reported in similar frequencies with diarrhea and nausea being the two most common events reported for both groups. The most common drug-related events (>2%) for both treatment groups are summarized in Table 4.

Of the adverse events reported, most were categorized as mild/moderate (90% moxifloxacin, 94% azithromycin) and improved or resolved without intervention. Study drug was prematurely discontinued due to one or more adverse events in six moxifloxacin-treated patients (no one event predominated). Five of these six discontinuations were considered to be possibly/probably-related to study drug (e.g., facial numbness, headache, lightheadedness, dizziness, anxiety, nausea, vomiting). The sixth patient was discontinued because of severe asthma unrelated to the study drug. There was one death in this study, unrelated to study treatment, in the azithromycin group, due to a cerebrovascular accident that was preceded by a myocardial infarction.

Sixteen patients had one or more serious adverse events, nine in the moxifloxacin group and seven in the azithromycin group (including the death). These events included: asthma, gastroenteritis, anxiety, carcinoma, pancytopenia, sepsis, fever, pneumonia, bronchitis, myocardial infaction. Only the asthma exacerbation resulted in study drug discontinuation but was not considered to be related to study drug treatment.

Discussion

Identification of the bacterial etiology of lower respiratory infection and knowledge of antimicrobial susceptibility is the ideal approach to selecting antimicrobial treatment. However, the advent of managed care has limited the physician's ability to isolate and identify the common respiratory tract organisms that infect the AECB patient residing in the community because culture and susceptibility testing are no longer routinely permitted. While re-evaluation of this practice is necessary, empirical antimicrobial therapy that is safe and effective for the anticipated pathogens, with consideration of local resistance patterns, must be prescribed. Selection of the appropriate antimicrobial has recently become more challenging with the increasing incidence of beta-lactam and macrolide-resistant *S. pneumoniae* and beta-lactamase-producing *H. influenzae* (10–15).

Our study was designed to establish the effectiveness of 5-day moxifloxacin compared to 5-day azithromycin in patients with AECB, including those with a proven bacterial etiology. Patients were carefully evaluated and stratified based on severity of illness. Because antimicrobial therapy has been shown to be of benefit for the sicker patients (8), predominately patients with type I AECB were enrolled. We found that clinical response at the test-of-cure visit was 88% for both the 5-day moxifloxacin-treated patients and the patients given azithromycin for 5 days. Similar clinical cure rates were observed for those patients with a confirmed infectious etiology (88% *vs.* 86%, respectively). Amongst those considered clinically-valid, moxifloxacin therapy was associated with fewer superinfections and reinfections when compared to those given azithromycin. Although bacteriologic eradication rates for individual organisms were similar for both treatment groups, at the end of therapy visit moxifloxacin eradicated 100% of the five most common pathogens (*H. influenzae, M. catarrhalis, H. parainfluenzae, S. pneumoniae, S. aureus*), whereas eradication following azithromycin ranged from 77% to 100%. A potentially important clinical difference in eradication rates was seen at the test-of cure visit where 22% of azithromycin patients had a persistent *Haemophilus* spp. pathogen compared to only 6% persistence in moxifloxacin-treated patients.

This study corroborates several earlier investigations which demonstrate that moxifloxacin is an effective agent for the management of patients with AECB (19–21). A recent study by Chodosh *et al.* compared the efficacy and safety of moxifloxacin to clarithromycin for the treatment of >900 patients with bacterial proven AECB (19). Clinical resolution was reported in 89% of 5-day moxifloxacin-, 91% of 10-day moxifloxacin-, and 91% of clarithromycin-treated patients. Corresponding bacteriologic eradication rates were 89% for 5-day moxifloxacin, 91% for 10-day moxifloxacin, and 85% for the clarithromycin group. For *S. pneumoniae*, in particular, 5-day and 10-day moxifloxacin regimens eradicated 100% and 95% of organisms, respectively, compared to 91% in the clarithromycin group.

Wilson *et al.* compared the efficacy and safety of moxifloxacin to clarithromycin among 745 patients with AECB (20). Of importance, resistance of pretherapy organisms was only reported for clarithromycin, with 15% of all isolates being clarithromycin-resistant. Although clinical cure rates were similar between moxifloxacin and clarithromycin (~88% each), moxifloxacin was associated with a statistically higher bacteriologic eradication rate (77% *vs.* 62%, respectively).

A recent meta-analysis of >2000 patients with AECB who received treatment with either moxifloxacin or a comparator agent (clarithromycin or cefuroxime axetil) found that moxifloxacin had higher end of therapy clinical and bacteriologic success rates (each 95%) *vs.* the comparator group (85% to 92%) (21). Specifically, bacteriologic eradication rates for the comparator antimicrobials against *S. pneumoniae* (92% clarithromycin, 90% cefuroxime axetil) and *H. influenzae* (72% clarithromycin, 88% cefuroxime axetil) were lower compared to moxifloxacin (>96%).

Although the standard duration of antimicrobial therapy for AECB of bacterial origin has ranged from 10 to 14 days, the optimal length of therapy is still being defined (4). Several studies, some including fluoroquinolones, have evaluated shorter course regimens (3–10 days) with reasonable success rates (19,22–25). The Chodosh study described above was pivotal in suggesting that 5-day moxifloxacin was effective for ABECB (19). Our data also confirm that 5-day moxifloxacin therapy is effective for the treatment of ABECB.

Because morbidity can be extremely high in patients with AECB, the time to improvement is important when considering antimicrobial options. In our analysis of the rate of bacteriologic eradication among a single center subset of our patient population, we found that 63% of moxifloxacin-treated patients showed eradication of their pathogen by day 3 of therapy compared to 48% of patients in the azithromycin-treated group at the same time point. Moreover, while none of the moxifloxacin-treated patients had persistent organisms at the end of therapy, 15% (four of 27) of the azithromycin-treated patients still had evidence of bacteriologic persistence. The importance of these findings requires further validation, and such studies are now underway.

In the current trial, both moxifloxacin and azithromycin were well-tolerated. We found that the most common adverse events for both the 5-day moxifloxacin and azithromycin regimen were gastrointestinal-related (e.g. diarrhea). Very few patients discontinued study drug prematurely due to an adverse event and the majority of drug-related events were of mild to moderate intensity and none required interventions.

In summary, this trial has shown that patients with AECB can be safely and effectively treated with 5 days of moxifloxacin given once daily, without the need for a loading dose, compared to the typical 5-day regimen of azithromycin, which includes a loading dose. In addition, moxifloxacin can be administered with or without food without compromising the quinolone's pharmacodynamic properties and potential effectiveness. A short-course regimen of moxifloxacin is therefore an effective treatment option for patients with ABECB.

Acknowledgements

This multicenter trial was presented in part at ATS 2000, Toronto, Ontario, Canada, May, 5–10, 2000.

This work was sponsored by Bayer Corporation, Pharmaceutical Division, West Haven, Connecticut, U.S.A.

References

1. Celli BR, Snider GL, Haffner J, *et al*. ATS statement: standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; **152** (Suppl): S77–S120.
2. Ball P, Harris JM, Lowson D, Tillotson G, Wilson R. Acute infective exacerbations of chronic bronchitis. *Q J Med* 1995; **88:** 61–68.
3. Fuso L, Incalzi RA, Pistelli R, *et al*. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. *Am J Med* 1995; **98:** 272–277.
4. Chodosh S. Bronchitis and asthma. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases*. Philadelphia: W.B. Saunders Co., 1992; 476–485.
5. Monso E, Ruiz J, Rosell A, *et al*. Bacterial infection in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; **152:** 1316–1320.
6. Monso E, Rosell A, Bonet G, *et al*. Risk factors for lower airway bacterial colonization in chronic bronchitis. *Eur Respir J* 1999; **13:** 338–342.
7. Zalacain R, Sobradillo V, Amilibia J, *et al*. Predisposing factors to bacterial colonization in chronic obstructive pulmonary disease. *Eur Respir J* 1999; **13:** 343–348.
8. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; **106:** 196–204.
9. Saint S, Bent S, Vittinghoff E, Grady D. Antibiotics in chronic obstructive pulmonary disease exacerbations: A meta-analysis. *JAMA* 1995; **273:** 957–960.
10. Thornsberry C, Ogilvie P, Kahn J, Mauriz Y. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States in 1996-1997 respiratory season. *Diagn Microbiol Infect Dis* 1997; **29:** 249–257.
11. Doern GV, Jones RN, Pfaller MA, Kugler K, Sentry Antimicrobial Group. *Haemophilus influenzae* and *Moraxella catarrhalis* from patients with community-acquired respiratory tract infections: antimicrobial susceptibility patterns from the SENTRY antimicrobial surveillance program (United States and Canada, 1997). *Antimicrob Agents Chemother* 1999; **43:** 385–389.
12. Doern GV, Brueggemann A, Holley HP Jr, Rauch AM. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994–1995: results of a 30-center national surveillance study. *Antimicrob Agents Chemother* 1996; **40:** 1208–1213.
13. Doern GV. Trends in antimicrobial susceptibility of bacterial pathogens of the respiratory tract. *Am J Med* 1995; **99:** S3–S7.
14. Doern GV, Pfaller MA, Kugler K, Freeman J, Jones RN. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SENTRY Antimicrobial Surveillance Program. *Clin Infect Dis* 1998; **27:** 764–770.
15. Thornsberry C, Ogilvie P, Holley HP Jr, Sahm DF. *In vitro* activity of grepafloxacin and 25 other antimicrobial agents against *Streptococcus pneumoniae*: correlation with penicillin resistance. *Clin Ther* 1998; **20:** 1179–1190.
16. American Thoracic Society. Chronic bronchitis and asthma, and pulmonary emphysema. A statement by the committee on diagnostic standards for non-tuberculous respiratory diseases. *Am Rev Respir Dis* 1962; **85:** 762–768.
17. *Performance Standards for Antimicrobial Disk Susceptibility Tests*. 5th Edn. Approved Standard. M2-A5. Villanova, PA: National Committee for Clinical Laboratory Standards, 1993.
18. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*. 3rd Edn. Approved Standard. M7-A3. Villanova, PA: National Committee for Clinical Laboratory Standards, 1993.
19. DeAbate CA**,** Herman-Gnjidic Z, Aneiro-Stotler L, *et al*. Moxifloxacin in acute exacerbations of chronic bronchitis—a bacteriological meta-analysis. Abstract P351. In: *Proceedings of the 21st International Congress of Chemotherapy*. Birmingham, UK: July 4–7, 1999.
20. Wilson R, Kubin R, Ballin I, *et al*. Five day moxifloxacin therapy compared with 7 day clarithromycin therapy for the treatment of acute exacerbations of chronic bronchitis. *J. Antimicrob Chem* 1999; **44:** 501–513.
21. Krasemann C, Meyer JM, Springsklee M. Moxifloxacin (MXF) in acute exacerbations of chronic bronchitis (AECB)—a bacteriological and clinical meta-analysis. Abstract P0203. In: *Proceedings of the 9th European Congress of Clinical Microbiology and Infectious Diseases*. Berlin, Germany: May 21–24, 1999.
22. DeAbate CA, Russell M, McElvaine P, *et al*. Safety and efficacy of oral levofloxacin versus cefuroxime axetil in acute bacterial exacerbation of chronic bronchitis. *Respir Care* 1997; **42:** 206–213.

23. Habib MP, Gentry LO, Rodriguez-Gomez G, *et al*. A multicenter, randomized study comparing the efficacy and safety of oral levofloxacin *vs*. cefaclor in the treatment of acute bacterial exacerbations of chronic bronchitis. Abstract LM2. In: *Proceedings of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy*. New Orleans, LA: September 15–18, 1996.
24. Langan CE, Cranfield R, Breisch S, *et al*. The efficacy and safety of grepafloxacin 400 mg od or 600 mg od in the treatment of acute bacterial exacerbations of chronic bronchitis: Comparison with amoxicillin 500 mg tds. Abstract 410. In: *Proceedings of the 8th European Congress of Clinical Microbiology and Infectious Diseases*. Lausanne, Switzerland: May 25–28, 1997.
25. Hoepelman IM, Mollers MJ, van Schie MH, *et al*. A short (3-day) course of azithromycin tablets versus a 10-day course of amoxycillin-clavulanic acid (co-amoxiclav) in the treatment of adults with lower respiratory tract infections and effects on long-term outcome. *Int J Antimicrob Agents* 1997; **9:** 141–146.